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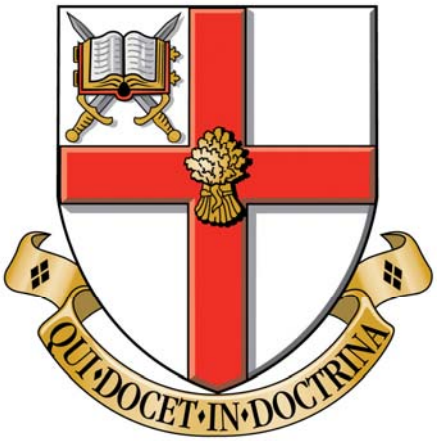

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Review

Prenatal exposures and exposomics of asthma

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Abstract: This review examines the causal investigation of preclinical development of childhood asthma using exposomic tools. We examine the current state of knowledge regarding early-life exposure to non-biogenic indoor air pollution and the developmental modulation of the immune system. We examine how metabolomics technologies could aid not only in the biomarker identification of a particular asthma phenotype, but also the mechanisms underlying the immunopathologic process. Within such a framework, we propose alternate components of exposomic investigation of asthma in which, the exposome represents a reiterative investigative process of targeted biomarker identification, validation through computational systems biology and physical sampling of environmental media.

Keywords: air pollution; prenatal; early-life; in utero; exposome; asthma; immune; metabolomics; indoor

1. Introduction

Childhood asthma represents a heterogeneous set of conditions, in which, functional lung impairment, chronic inflammation, tissue remodeling, and response to therapy represent some hallmark events. In spite of phenotypic differences, a number of international guidelines point to airway inflammation control as the primary goal of therapy [1]. Another key event of asthma features altered development of the cellular and molecular components of the immune system prior to the appearance of the asthmatic phenotype [2].

1.1. Burden of childhood asthma

Allergic asthma, allergic rhinitis, and eczema represent the most common childhood chronic diseases in the industrialized world [3]. Worldwide, the mean prevalence of asthma is estimated to range between 5 and 25% for 6–7 age group [4], reflecting plateauing of prevalence within many industrialized countries. Worldwide, the mean prevalence of asthma is estimated to range between 5 and 25% for the 6–7 age group [4], reflecting plateauing of prevalence within many industrialized countries [4,5]. Within United States (US), an estimated 13 ± 0.4% of African American, 13 ± 1.7% of American Indian/Alaska Native, and 8 ± 0.2 % of White children suffer from asthma [6].

The economic toll of living with asthma is estimated at $37.2 billion for 2007 in the US alone[7]. An estimated 10.5 million school days were missed due to asthma between 2005–2009 [8]. Furthermore, the burden of asthma is disproportionately greater for low income and minority children[9].

In spite of intensive on-going investigations on genetic [10], environmental [11], and lifestyle-related [9] risk factors, true causal processes remain unknown [12]. Known multiple classical allergens and adjuvants to date, including infiltrated ambient air pollutants, cockroach and cat dander, dust mites, mice allergens, and environmental tobacco smoke (ETS), do not adequately explain the burden of asthma in children [13,14]. Furthermore, current efforts have failed to stem the growing worldwide development of childhood asthma [15,16]. To date, early-life mechanisms underlying the childhood asthma phenotype remain inadequately defined [15,16,17].

1.2. Aim and scope of this review

Within this review, we examine the early-life exposure to emerging classes of environmental pollutants and their role in respiratory and immune system impairment. As pregnancy is often associated with longer daily hours spent within the indoor environment, the scope of this review is limited to environmental pollutants that pregnant women are exposed to within their residential indoor environment. Within this context, we also examine limited sunlight exposure and the resulting low level of vitamin D as a behavioral sequela of large daily hours spent within the indoor setting. Therefore, we focus here is the combined contributions of gestational vitamin D deficiency and indoor environmental pollutant exposures on pre-clinical immune functional impairments during the first few years of a child's life. Specifically, our goal is to assess the internal validity of exposomic approaches to clarify the mechanisms underlying developmental impairments of the immune system. Here we are concerned with the segment of the population which includes non-occupationally exposed pregnant women with a low risk of adverse birth outcomes. Thus, specific occupational exposures to physical or chemical respiratory risk factors lie beyond the scope of this analysis. Furthermore, classical risk factors, including specific genetic susceptibility contributors, viral, fungal and bacterial agents within the indoor environment, maternal nutritional qualities (such as low dietary intake of vitamin D), social- and/or economic- stresses, have already been examined in a number of other excellent reviews[11,18,19,20]. The risks of classical allergens and adjuvants will not be assessed within the present review.

Based on the above considerations and within the context of asthma investigations, we assess the applicability and adaptability of the "exposomic approach" as a set of tools for a comprehensive exposure history characterization and as a health diagnostic tool for parents and infants. As previously

defined [21], the exposome is all exogenous factors (the environment) that can modify the endogenous host characteristics (genes and metabolic activities) that together influence health. The endogenous influences have been expanded to include the microbiome and the chimeric associations of pregnancy. For example, children with autism spectrum disorders (ASD) as well as maternal allergies, matenal psychological and socioeconomic difficulties, chemical, and biological (e.g. infection) stress during the pregnancy could contribute to increased risks of airway symptoms [22]. Interestingly, boys (6–8 years of age) have more doctor-diagnosed asthma and ASD than girls [22].

This review is composed of three sections. First, we lay the contextual framework of our discussion in terms of prenatal exposure to air pollution within a home indoor setting and its risks on asthma. Secondly, we examine the state of knowledge regarding exposure and outcome relationship. Thirdly, we propose novel components for exposomic investigation in light of the current gaps in knowledge regarding exposomic approaches as well as the future research direction for asthma biomarker validation.

2. Methods

A PubMed search was conducted using the search terms, asthma, immune, inflammation, oxidative stress, reactive oxygen species, lung, impairment, indoor, air pollution, prenatal, and childhood for peer-reviewed, primary research publications in the English language.

3. Results and Discussion

3.1. Home: context of in utero exposures

A substantial body of epidemiological evidence demonstrates that the indoor environment during early-life is critical to the occurrence of childhood asthma [11,23,24]. Children whose parents or caretakers report qualitative indications of indoor dampness, mold, poor ventilation, and recent home redecoration are at significantly greater risks of asthma and allergies [13,24,25]. Exposure within the indoor environment is compounded by energy conservation efforts for buildings, which reduce air exchange rates and promote indoor moisture buildup [26]. Home indoor dampness is estimated to be present in > 70% of the homes in upstate New York [27] and in > 50% of the homes in Europe [28]. Both adults and children spend an estimated > 90% of their daily hours within an indoor setting [29]. Within a vulnerable segment of the population (e.g. elderly, pregnant women, and young children), the exposure to indoor toxicants are estimated to be higher because of sedentary behavior[29]. However, while qualitative reporting of dampness is an established risk factor of asthma, home indoor dampness overall poorly correlate with directly measured fungi, mycotoxins, and other biogenic markers [30]. Furthermore, a growing body of investigations has failed to demonstrate an association between directly measured fungal components and asthma [14,24]. Recent reviews point out the critical need for the identification of specific etiologic agents underlying the surrogate marker of dampness in asthma and allergy investigation [11,25].

The exact mechanism through which a damp environment increases the risk of asthma inception and other lower airway allergic diseases remains unknown [23,24]. Another emerging line of evidence suggests home indoor dampness is correlated with modern chemicals [31]. Within a non-occupational setting, both new and degrading building structural material with polyvinyl chloride (PVC) has shown

to initiate or exacerbate asthma [32,33,34]. Sources such as PVC flooring or phthalate concentration in dust are significantly associated with a risk of asthma diagnosis [22,35]. Occupational exposure to painted surfaces have long been associated with eye irritation, skin itching, obstructive airway problems, and frequent urination in longitudinal follow-up studies [36,37,38,39,40,41].

However, exposure assessment of specific chemicals remains challenging. Data regarding temporal variability of the sources, emission, and human behaviors, and resulting human exposure remain scarce. The home indoor volatile organic compound (VOC) concentrations could persist or regenerate within the home indoor environment, aided by poor ventilation, humidity, and/or temperature variation in the indoor setting.

3.1.1. Propylene glycol and glycol ethers, the forgotten endocrine disruptors

A robust body of literature suggests that volatile organic compounds associated with cleaning tasks increases the risk of doctor-diagnosed asthma. Among the occupationally exposed adults, indoor sources such as cleaning spray, cleaning liquids, mechanical floor scrubbing, and window cleaning were significantly associated with risks of newly-onset asthma and other respiratory diseases[13,37,42,43,44,45]. Within a non-occupational setting, the children, whose homes had the highest 25% of propylene glycol and glycol ethers (PGEs) concentrations, had a 2.0-fold greater likelihood of having doctor-diagnosed asthma (95% CI, 0.9–4.4), a 4.2-fold greater likelihood of rhinitis (95% CI, 1.7–10.3), and a 2.5-fold greater likelihood of eczema (95% CI, 1.1–5.3) [46].

PGEs are globally distributed as organic solvents and coalescents within cleaning agents, paints, pharmaceuticals, inks and consumer products (e.g., cosmetics, PVC, and glue) [40,47,48]. In various animal models, PGEs cause male sub-fertility and infertility, an increased time to pregnancy [49], oocyte depletion, spontaneous abortion, hematopoietic, immune (e.g., thymic) function suppression in adults, and transplacental fetotoxicities [48].

3.1.2. Other volatile organic compounds of mistaken origin

To date, a great deal of confusion exists regarding the true sources of common VOCs of indoor origin [50,51]. For example, 1-octen-3-ol and 1-butoxy-2-propanol are traditionally known as microbially emitted VOC [50]. However, recent work suggests that they are more likely to be emitted from PVCs at home, glues and other building structural material To date, a great deal of confusion exists regarding the true sources of common VOCs of indoor origin [50,51]. For example, 1-octen-3-ol and 1-butoxy-2-propanol are traditionally known as microbially emitted VOC [50]. However, recent work suggests that they are more likely to be emitted from PVCs at home, glues and other building structural material [36]. Furthermore, 2-ethyl-1-hexanol is traditionally known as MVOC and a “sick building syndrome” compound [52]. However, 2-ethyl-1-hexanol could also be produced as a by-product of di-2-ethylhexyl phthalate (DEHP) degradation [53]. 2-ethyl-1-hexanol from newly painted home indoor surfaces are significantly associated with asthma symptoms and airway inflammatory symptoms in a population-based survey of adults [52]. Another common plasticizer, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TMPD-DIB, also known as TXIB) possesses adjuvant properties, including allergic airway inflammation, heightened production of IL-12, and oxidative stress in allergen sensitized mice [32]. 2,4-trimethyl-1,3-pentanediol monoisobutyrate (TMPD-MIB, also known as Texanols^{TM}) is globally distributed coalescing agents in latex (i.e. water-based) paints,

print-ink, and PVC flooring material [54]. Non-occupational exposure to TXIB and Texanols™ in the general population is a concern because they are detected in considerable concentrations in ambient air in the city of Los Angeles [54], newly painted and installed housing units [55,56,57], and in food packed in polystyrene and polypropylene cups [58]. Furthermore, both TXIB and Texanols™ represent some of the most common VOCs within the temporary housing units constructed by the US Federal Emergency Management Administration for the families displaced by Hurricane Katrina in 2005 [56].

3.1.3. Secondhand smoke exposure(SHS)

SHS is a well-known risk factor for asthma [59]. Second-hand smoke (SHS) is composed of > 4000 chemicals, some of which are mutagens/carcinogens, developmental toxicants, and irritants [60]. Prenatal exposure to ETS has been associated with adverse effects on fetal and child growth [61] and cognitive functioning during childhood [62], as well as exacerbation of childhood asthma and with allergic response [63]. Furthermore, SHS is a primary delivery mode of other VOCs, including benzene, toluene and styrene in the US population [64].

3.1.4. Vitamin D

Higher confinement to indoor life (and associated deprivation from sunlight) can lead to vitamin D insufficiency with concomitant increases in exposure to indoor pollutants. A vitamin D deficiency is associated with chronic lung disease [65], which likely relates to less control of the inflammation and oxidative stress induced by the indoor air. Vitamin D insufficiency (serum level of 25(OH)D < 30 ng/mL) is common among children in the United States [66,67]. Among children aged 6–11 years, vitamin D deficiency was approximately 62% in non-Hispanic whites, approximately 86% in Hispanics, and approximately 96% in non-Hispanic blacks [66]. Prior work has shown that Vitamin D deficiency leads to impaired Th1 and Th17 lymphocyte function [68]. Furthermore, it has also been associated with reduced activity of FoxP3 functions in T_{reg} cells [68]. Low serum 25(OH)D has been strongly implicated in asthma due to its correlation with oxidative stress, resultant tissue damage, and airway inflammation [69]. In addition, cytokine production of cord blood T cells is correlated with season [67,70]. Thus, season could influence the exposure to home indoor toxicants by promoting the family members to reduce the home ventilation rate, nutritional intake of food items rich in vitamins (e.g., spinach, kale, collards, soy beans, and rainbow trout), sunlight (thereby, vitamin D) or maternal infection, as well as the asthma outcome [67,70].

3.2. Childhood immune markers and asthma risks

3.2.1. A definition of immune system impairment

Developmental alterations during early life in the immune system is thought to underlie subsequent allergic diseases [71]. A hallmark of such pre-clinical events consists of preferential enhanced development of the $CD4^+$ type-2 helper T cells (Th2) [72]. Within this review, we narrow the scope of altered immune system development as skewed T-cell differentiation, including Th1, Th2, Th17 and regulatory T (T_{reg}) cells, and innate immune cells.

3.2.2. Biomarkers of immune system impairments

Several indoor environmental exposures to modern chemicals (from building material, consumer product uses, and lifestyle) within a damp home indoor environment (contributed by structural water damage, poor ventilation, and/or low temperature) have been shown to contribute to altered development of fetal innate and adaptive immune cells [34,73,74,75,76]. A critical event in this process is the unbalanced development of Th1 and Th2 cells [72]. The Th2 phenotype naturally dominates during fetal development, but environmental pollutants are suggested to maintain or enhance this imbalance after birth. Accordingly, unclear events preceding Th1/Th2 imbalance and identification of high risk newborns represent key barriers to our understanding of this process [71]. An improved understanding of prenatal exposure to indoor synthetic pollutants and the risks on prolonging the Th1/Th2 cell imbalance represents the main challenge to aid interventions, which limit risks during pregnancy.

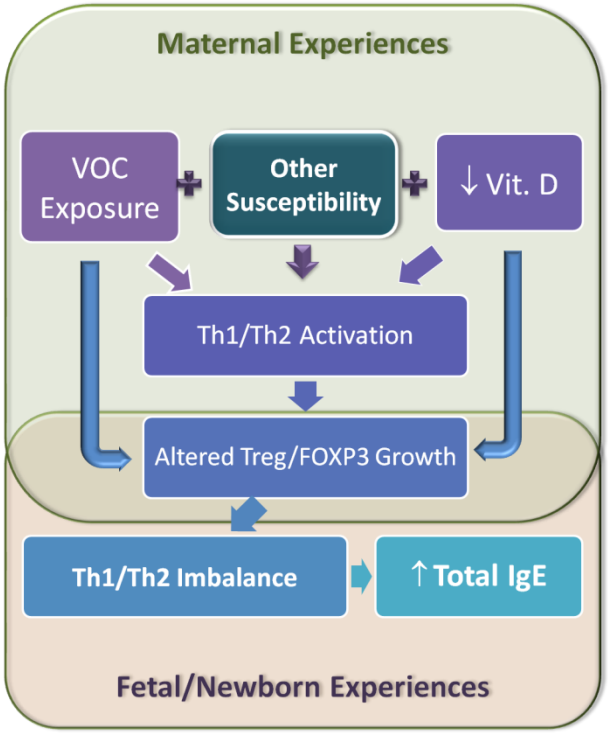

Figure 1. Proposed conceptual model.

A conceptual framework of our work is outlined in Figure 1. Multiple-hits on the maternal immune system from home indoor exposure to VOCs, other susceptibilities (i.e., maternal anthropomorphic traits, maternal and paternal atopy, secondhand smoke, and season), and low vitamin D level, activate innate immune cells (e.g., NK cells, macrophages, neutrophils). Such multiple-hits promulgate inflammation and resultant oxidative stress, further skewing maternal T cells toward Th2 development [77], while suppressing T regulatory (T_{reg}) cells and the associated Foxp3 gene expression [78]. Suppression of maternal T_{reg} cells, in turn, leads to an unbalanced development of cytokines produced by the Th1, Th2 cells as markers of pre-clinical, immunotoxic consequences in newborns. Here, we posit that Th2 cells, which release interleukin (IL)-4, IL-5, and IL-13 promote

asthma. Increased IL-4 production heightens the IgE level, which arms mast cells and basophils for their detrimental allergen-induced release of bronchoconstrictor mediators [79]. IL-5 increases the presence of eosinophils [79] and IL-13 increases bronchoconstriction. Therefore, environmental factors that cause a Th1-Th2 imbalance in the prenatal or early postnatal period, in particular, T-cell polarization toward Th2 reactivity, may contribute to the risk of allergic disease. Genetic associations have also connected asthma, inflammation, and atopy [80], which further supports our proposed analysis of the associations of environmental exposures, immune biomarkers, and asthma severity.

3.3. Exposome

There are three biosystems (maternal, fetal, and placental), which need to be considered for the exposomic investigation of prenatal effects. Each of these biosystems has an influence on the health of offspring for their lifetime after maternal exposure to environmental stressors. The placenta is grouped as a separate entity, because it is not a permanent organ of either the mother or offspring, it is an intertwined mix of maternal and fetal cells, and its physiological presence is vital for fetal existence. The lifetime consequences of developmental exposures modulate both the immunity [81,82] and behavior of offspring [83,84]. The exposomal composite [21,85,86] begins at conception, but the constant and consistent interplays of environment and genetics affect health throughout the lifetime. Developmental exposomics includes the analyses of all exogenous environmental (biological, chemical, and psychological/physical) stressors on these three biosystems and the resultant effects on endogenous cellular and molecular activities, which affect health. These include the body's dynamic adaptation, repair, or further damage in response to the varying environmental influences [87]. The effects of prenatal exogenous stressors and the endogenous responses to the environmental modulators, which depend on the fetomaternal genotypes, determine whether a disorder/disease will occur with greater prevalence within the lifetime of the offspring. The exposome paradigm suggests that pollutants must be evaluated with consideration of the additive, synergistic and "potentiated" affects from all environmental influences, including diet and life-style behaviors, which includes psychological and physical stress, and that the environmental influences are dependent on each person's genetics [88]. Consideration of potentiated effects are especially important for exposomic analysis since two different stressors may induce no detectable effect on separate pathways, but these pathways converge leading to a detrimental response [84].

As the fetus develops, the metabolomics [89] and proteomics of the mother, placenta (the interconnecting fetomaternal barrier) and fetus regulate the constituents for fetal growth and differentiation. At conception and later in gestational development, environmental stressors, including air pollutants, have been reported to affect the prevalence of asthma in the offspring [90,91]. It seems somewhat incongruous that an air pollutant, which affects the maternal lung could affect fetal development. However, some pollutants may directly permeate to the placenta and fetus and other pollutants may induce endogenous maternal cellular and molecular changes that transmit the lung exposure to the placenta and fetus [92,93,94]. It is especially interesting to note that mast cells in the lung interstitium and alveolar epithelium and in close proximity to the vascular and nervous system networks are implicated in asthma, because mast cells also play an important role in placenta development. The airways of asthmatic individuals have increased presence of mast cells, and mast cells have been suggested to enhance the asthmatic pathology [95,96,97]. Mast cell release of histamine and proteases occurs with ozone exacerbation of asthma [98,99,100,101,102]. Mast cells are

often considered to play a role in allergic asthma with regard to antigen-specific allergen triggering via IgE. However, mast cells and other innate immune cells can enhance asthma with pattern recognition receptor (PRR)-induced release of prostaglandins and other inflammatory factors due to exposure to pathogen-associated molecular patterns (PAMPs). The involvement of innate immune cells in asthma may be one reason why inhaled corticosteroids (ICS) sometimes have little effect, in that ICS have minimal influence on the number of mast cells in asthmatic lungs [103] and on bronchoconstriction[104].

Air pollutants can modulate placenta structure and function [105,106,107,108,109], including immune activities associated with the placenta [110]; thus, it is not surprising [110]; that they either directly affect the placenta and fetus or rely on transited maternal cells and molecules. Hematopoietic mast cells have been suggested to play a role in implantation and placenta development [111,112], which affects offspring birth weight. Mast cell activity and other immune activities in the placenta affect placenta size, which can affect birth weight. Mast cells [113] and air pollutants [113] and air pollutants [114,115,116] also have been linked to preeclampsia. The placenta controls bidirectional trafficking of cells and molecules, and thus plays an intermediary role in the fetomaternal relationship.

Asthma is a multifaceted inflammatory disease of the airways that usually includes increased mucus production, bronchorestriction, and airway remodeling. Whether asthma is classified as allergic or non-allergic immune cells producing similar cytokines and chemokines are implicated. Allergic asthma involves mainly adaptive lymphocytes including $CD4^+$ Th2 cells producing IL-4, IL-5, and IL-13. IL-4 promotes B lymphocyte switching to the IgE antibody isotype, which arms mast cells and basophils with antigen-specific signaling. IL-5 promotes the growth and differentiation of eosinophils, and IL-13 promotes contraction of airway epithelial cells and smooth muscle cells. Non-allergic asthma involves innate lymphocytes of different classes referred to as innate lymphoid cells (ILC)1, ILC2 and ILC3 [117], which respond to PAMPs with their PPRs and produce IL-4, IL-5, IL-13 and IL-17. The fetomaternal condition skews both the mother's and fetus's helper T cells toward the Th2 phenotype via epigenetic modulations as the naïve T cells are induced to proliferate. As the offspring gets exposed to the non-aseptic environment at birth further epigenetic modulation generally leads to a more balanced ratio of Th1 and Th2 cells; however, prenatal and postnatal environmental influences, including ozone, cigarette smoke, diesel exhaust and other airborne pollutants seem to enhance the continuation of the Th2 dominance [118]. With regard to allergic asthma the enhanced maintenance of the Th2 imbalance may be due to the phenotype of the antigen presenting cells (APCs). Alternatively, activated macrophages or M2 macrophages or dendritic cells preferentially activate Th2 cells. Oxidative stress from pollutants can lower the amount of cellular glutathione (GSH, the cell's main anti-oxidant) and APCs with less GSH preferentially activate Th2 cells [118,119,120]. Interestingly, GSH loss has been implicated in the induction of asthma due to numerous airborne metabolites exposures that can generate oxidative stress [121]. Prenatal exposure to acetaminophen also influences the risk of wheezing incidence at age 5 due to GSH variance [122]. Oxidative processes from prenatal exposures to cigarette smoke [123,124], polycyclic aromatic hydrocarbons [125], PCBs [126], phthalates [127], and bisphenol A [128] are likely due to aryl hydrocarbon receptor (AHR) activation[129], which promotes inflammation and asthma; these pollutants are known to activate AHR [129,130].

Allergic asthma is often of low or moderate severity with a relatively low level of airway remodeling although it is as chronic as the more severe form. Severe asthma with more recurrent exacerbations usually involves a greater extent of inflammation with a greater presence of neutrophils

and eosinophils. Severe asthma also includes more IFNγ and IL-17 from Th1 and Th17 cells or ILC2 and ILC3 cells. The ILC2 and ILC3 subsets are lineage negative cells; whereas, the ILC1 subset includes NK cells. ILC2 and ILC3 cells are IL-7R positive; IL-7 is produced by hematopoetic stromal cells, and it supports early lymphoid progenitor differentiation of the stem cells. The ILC2 population is very similar to the Th2 population with regard to its cytokine profile; it develops in the presence of IL-25 and IL-33, and like Th2 cells, it expresses the GATA-3 transcription factor. IL-33 is a nuclear protein released by airway epithelial cells damaged by airborne pollutants; it is referred to as a damage-associated molecular pattern molecule (DAMP) or as an alarmin and is activated by cleavage with mast cell protease [131]. Th2 and ILC2 cells, mast cells, basophils and eosinophils are stimulated by IL-33. Another stimulator of ILC2 cells is thymic stromal lymphopoietin (TSLP) [132], which like IL-33 is released from airway epithelial cells and smooth muscle cells [133]. Damaged airway cells also release ATP [133]. Damaged airway cells also release ATP, which recruits and activates mast cells[134,135]; via ATP-induced activation of the inflammasome, cleaved active form of IL-1β is produced [136], which also recruits neutrophils and Th17 cells, and inflammation and airway remodeling is enhanced [137].

3.3.1. Utility

Attraction and promise of Exposome-Wide Association Studies (EWAS) lie in distinguishing biomarkers of exposure from biomarkers of disease phenotype [88,138]. Recent blood-based exposomic analyses have shown their potential to capture multiple environmental factors, including the nutrients [139], viral infection [140], the microbiome [141], stress [142], and environmental toxins[143]. For example, preterm delivery as well as fetal growth restriction has been shown to be associated with urinary levels of acetate, tyrosine, formate, trimethylamine, lysine and glycoprotein [144].

Rappapport (2012) proposes a two-phase strategy for exposomic investigation of the disease outcomes. Within the first phase, molecules are scanned through an agnostic search tool for their association with the disease outcome status [138]. The second stage investigation is often directed to investigate the role of the metabolites (identified in the first phase) as causal contributors or intermediate players in pathophysiology of the clinical phenotypes [145]. The first phase of the analyses is often conducted through liquid-chromatography tandem mass spectrometry (LC-MS/MS) or nuclear magnetic resonance (NMR) spectroscopy [146]. Each has advantages and shortcomings. LC-MS offers the advantage of greater sensitivity of molecules in biofluids (e.g., ~4000 molecules within plasma sample) and better molecule discrimination [146]. On the other hand, NMR detect[146]. On the other hand, NMR detects relatively smaller set of particles (< 200). But, the NMR does not destruct the sample, thus permitting repeated analysis [146]. Furthermore, application of LC-MS/MS is also limited by the fact that existing libraries are too small to identify most of the detected molecules[147]. To date, interpretability of many metabolomics analyses remain extremely limited due to fragmentations or adduct formations [148]. To date, statistical methodology regarding pattern recognition remains the major challenge associated with metabolomics analysis. The challenge lies not only in the association of biomarkers with the disease outcome of interest, but also in clarifying the relevance of a given biomarker in a pathophysiological process [145]. Given the preliminary nature of small molecular biomarkers for phenotypic analyses, independent validations in order to account for the high-dimensionality of the analyses and the associated false discovery rates represent critical steps in identification of true disease outcome markers [138].

3.3.2. Urinary metabolomics

Metabolomics captures a comprehensive catalogue of small molecules (molecular weight < 1500 Daltons) within any organic systems or physiological state [149]. Urine metabolomic profiling holds promise as a non-invasive and unbiased window to the "sum of history" of the present disease status for newborns and children [145]. For example, within a murine model of asthma, administration of dexamethasone induced a marked, yet, reversible metabolism of carbohydrate, lipid, and sterol in bronchoalveolar lavage fluid from asthmatic lungs [149].

Within a clinical setting, the urinary metabolic profile of preterm and term infants were distinctly unique according to the gestational age at delivery [150]. In particular, preterm status was associated with altered patterns of: 1) tyrosine metabolism; 2) the biosynthesis process of tyrosine, tryptophan, and phenylalanine; 3) urea cycle; 4) arginine metabolism; and 5) proline metabolism [150]. Furthermore, co-morbid condition of extremely low weight as well as preterm delivery status was associated with altered arginine-proline metabolism, purine-pyrimidine metabolism, and urea cycle during adulthood[150]. In another pilot investigation of children with nephron-uropathies (renal dysplasia, vesico-ureteral reflux, urinary tract infection, or acute kidney injury) versus healthy children, the disease status was associated with an alteration in the urea cycle as well as purine and pyridine synthesis [150]. Metabolic profiling of asthmatic versus healthy control children using liquid chromatography—mass spectrometry (LC-MS) demonstrated lower levels of urocanic acid and methyl-imidazoleacetic acid in the asthmatic children compared to the controls [148]. Both urocanic acid and methyl-imidazoleacetic acid play a role in inflammatory responses. Overall, the number of studies for the identification of the biomarker using this technology remains extremely limited due to the limitations in analytical chemical techniques as well as the computational and bioinformatic tools[145].

3.3.3. Predictive value of metabolomic profile for asthma

Undirected metabolomics refers to the comprehensive measurement of all small molecules within a given sample. Such data is subsequently cleaned into a small set of signals and qualitatively recognized through *in silico* searches of existing libraries or ionization experiments [151]. While this approach has [151]. While this approach has potential for the identification of novel biomarkers, a number of potential issues with such biomarkers have also been identified [145]. One of the critical issues relate to the erroneous identification of noise rather than a signal [145]. Even when a meaningful signal is detected, the biological relevance of the signal to underlying etiological process remains a challenge [145]. For example, Nuclear Magnetic Resonance (NMR) based metabolomic analysis applied to exhaled breath condensate demonstrated greater sensitivity to discriminate asthmatic children (86% sensitivity) compared to that based on exhaled nitric oxide and Forced expiratory volume (FEV_1) with 81% sensitivity [152]. However, the exact molecular identity could not be determined based on the NMR technique [152]. Thus, the issues of biological plausibility, reproducibility of the identified set (through second stage analysis) as well as confounding need to be addressed [145]. To date, most investigations have been able to identify only the biomarkers of clinical outcome status (e.g. cardiac ischemia) [145]. Thus, the development of predictive metabolomics biomarkers of disease outcome is needed as diagnostic tool.

In contrast, directed metabolomics refers to a more focused search of selected set of known and

expected metabolites using tandem mass spectrometry (MS/MS), or selected ion recording (SIR) with GC-MS [151]. Some investigators have used the targeted search as a validation tool for preliminarily identified set of metabolites [145].

3.3.4. Computational systems biology and its application to asthma

Computational modelling includes an array of quantitative techniques that can be used to assess health risk. The computational modelling offers the advantage of interpreting preliminarily identified signal in the second stage of exposomic investigation. Furthermore, the computational models could account for the underlying uncertainties inherent within complex biological systems and their response to environmental exposure. The type of model depends on the nature of the system to be modelled[153]. Historically, the physiologically based pharmacokinetic [153]. Historically, the physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model has been routinely employed in toxicological studies [154]. This approach uses an organism's toxicokinetic information to evaluate normal tissue limitations to chemical exposure (Figure 2). These models need information on the pollutants, including its absorption, distribution, metabolism, and elimination (ADME). In addition, information about the organ size, ventilation rates, the age, and the gender of the organism,

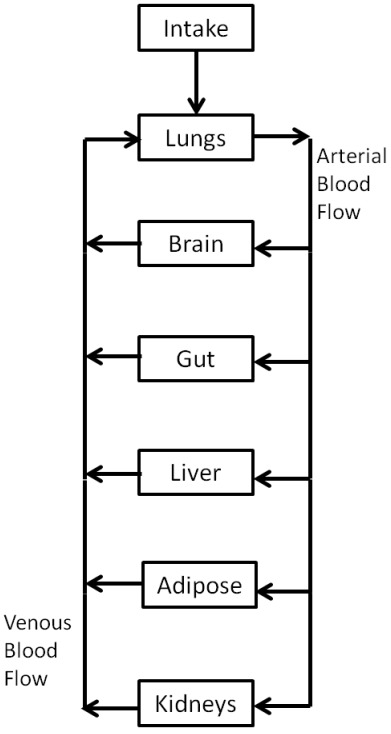

Figure 2. Generic structure of the PBPK modelling framework.

together with the hypothesized mechanistic information are required. PBPK modelling in early life has been used to determine toxicant exposure in children [155,156], however the focus has centered on drug metabolism and there is a paucity of models, which focus on environmental exposure and prenatal risk of developing asthma. In terms of prenatal exposures to toxicants, PBPK models have been used to quantify and characterize the physiological effects of drug exposure during pregnancy [157]. A

noteworthy development in PBPK modelling is the development human PBPK model toolkit by recoding published PBPK models [158]. This toolkit is expected to provide a straightforward reference point to a wide variety of models of this nature. The last decade and a half has also witnessed the growth of the systems biology paradigm as a framework for conducting toxicological investigations[159]. At the core of this new approach is computational systems biology [160]. The aim of computational systems biology is to use mathematics to describe complex biological phenomena in a quantitative manner using computer simulations (Figure 3). There is also an emphasis on using the models to study biological systems in a holistic manner as opposed the more reductionist approach that is often adopted in the wet-laboratory [161]. Several different mathematical approaches can be used when designing a computational systems model. These different mathematical approaches were recently reviewed in detail [162]. By far the most ubiquitously adopted mathematical approach is to use ordinary differential equations (ODEs). This method is similar in nature to PBPK models, in that, model reactions are informed by kinetic data and steady-state information about the biological system

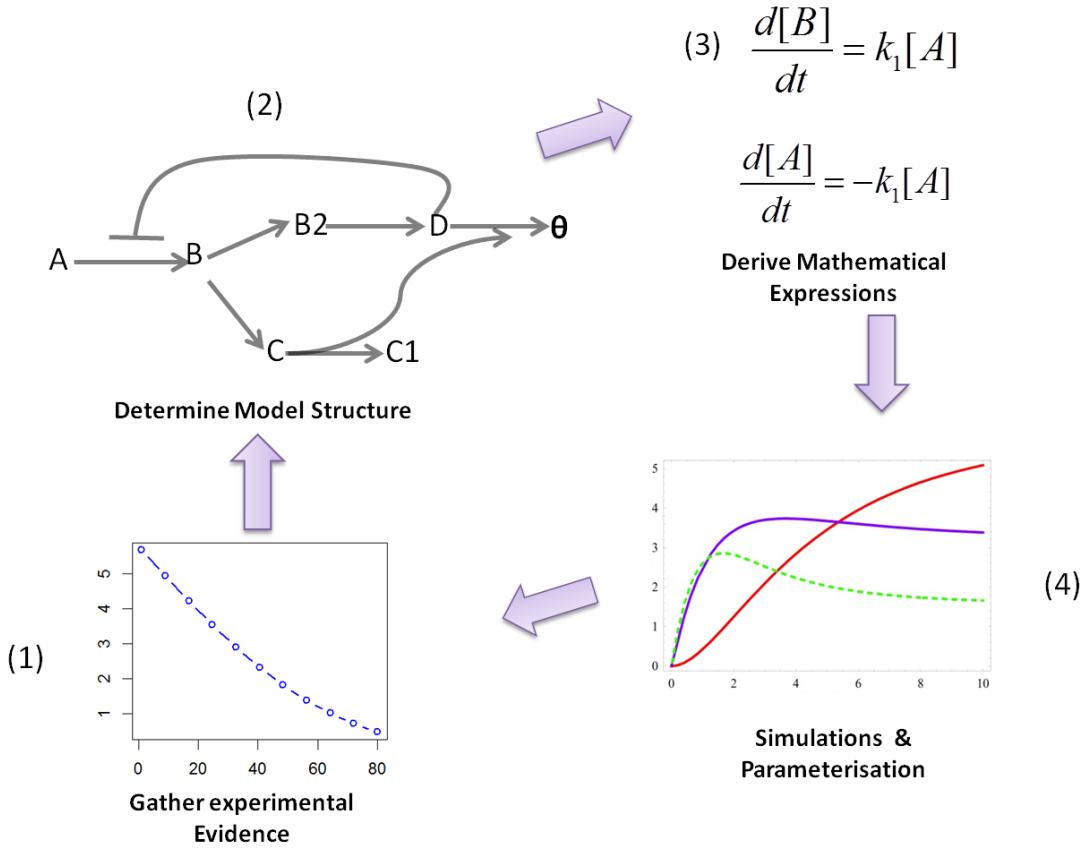

Figure 3. The steps involved in constructing a computational systems biology model.

under investigation. A disadvantage of these models is that they cannot include variability or spatial dynamics as part of the behavior of the biological system. Another disadvantage is that kinetic information is often difficult to obtain, despite a number of archives for online kinetic data [163]. Parameterizing such models is also challenging especially as the size of model increases [164]. A pertinent example of how an ODE model can dovetail with wet-laboratory experimentation is recent work by Carbo et al. (2014) which was used to investigate the role of interleukin-21 (IL-21) in the

gastric mucosa during *H. pylori* infection [165]. Computational systems modelling has been used to model $CD4^+$ T cell differentiation with *in vivo* mechanistic studies. The model predicted activated expression of T-bet and RORγt and the phosphorylation of STAT3 and STAT1 and suggested a potential role of IL-21 in the modulation of IL-10. This combined approach indicated that IL-21 regulates Th1 and Th17 effector responses during chronic *H. pylori* infection in a STAT1- and STAT3-dependent manner, and are thus regulators of the *H. pylori* infection. Of significance for this review is that it suggests *H. pylori* colonization protects against childhood asthma [166,167]. Therefore, this study outlines a way in which the immune system can be studied mechanistically by using a combined *in vivo in silico* approach. Stochasticity in systems models can be dealt with by using stochastic differential equations which represent biological reactions as discrete random molecular collisions. Such models often represent scenarios involving low molecule numbers such as protein molecules from an expression of a single gene [168]. The major disadvantage of such models is that they are computationally slow. Variability can also be represented by using Bayesian networks. This type of modelling is useful for making toxicant risk estimates [169]. Petri nets can also be used to construct a systems model. These are a special type of model which comprises of two nodes, called places and transitions. Places and transitions are connected using arrows. Each place contains a number of tokens which is the same as a discrete number of biochemical molecules. A Petri net functions by input- output firing at the 'transitions' within the network. The 'firing' of transitions represents a reaction taking place within a biological system [170]. There are a number of different standards for exchanging computational models, with the Systems Biology Markup Language (SBML) leading exchange format for the exchange of biological models at present [171]. This format is designed to be used for exchange independent of the modelling tool used to construct the model. Another more recent development from a purely toxicological perspective is the development of adverse outcomes (AOPs) [172]. AOPs are in essence are a way of having a mathematical representation which is informed by our current understanding of a biological pathway and how a change to that pathway could have an adverse outcome at the level of a whole organism or even population level [172]. Of note for this review is that this novel modelling methodology has been applied to studies which have investigated respiratory allergies [173]. The stages in building an AOP include determining the information required to represent the pathway of interest. A summary is then included in the form of a flow chart that depicts the AOP from molecular initiation even to its effect on the whole organism. The weight of the interaction is determined together with a confidence determination [174]. In light of developments such as those outlined in this section computational modelling will be applied further to both pre and post natal exposure to chemicals investigations.

3.3.5. Is external validation necessary within exposome?

In contrast to biomarker driven definition of exposome [138], the US National Research Council defines exposome as "the extension of exposure science from the point of contact between stressor and receptor inward into the organism and outward to the general environment, including the ecosphere"[175].

Within the context of asthma investigation, the more holistic definition proposed by the National Research Council is needed for the following reasons.

First, since most metabolomics studies have been of pilot-scale, validation of the biomarkers both within- as well as between-persons remains exceedingly rare. Furthermore, underlying

representativeness of the diseased versus healthy controls remains relatively poorly understood. For example, age-dependent appearance of the asthma phenotype requires validation of initial identification.

Second, temporal variability in external and internal exposures remains unknown [176]. At best, they are measured with substantial error [176]. Lack of valid and accurate exposure assessment data represents an important barrier to the understanding of true human exposure [11,13]. The nature of specific pollutants and the concentrations of presumed personal exposures remain unknown. In spite of these, predominant methodological approaches of asthma investigations rely on cross-sectional design[35,177,178,179]. Cross-sectional design is inherently limited in its ability to reject the possibility that risk factors (e.g. water-based cleaning) were adopted following the health outcome occurrence. In addition, most investigations rely on surrogate exposure markers and memory recall of potential sources (e.g., damp spots in ceiling, specific product uses, the history of renovation, or flooding) rather than direct measurement [13,24,25].

4. Conclusion

An improved understanding of the mechanistic processes underlying immune system impairments, early detection, and source removal are critical for prevention of asthma as a globally burdensome group of illnesses. This review considered damp home environments, emission and/or retention of VOCs from cleaning chemicals, latex paints, adhesives, rotting plasticizers, other aging furniture and structural material in homes as a context for exposure during early-life. We propose consideration of context of exposure within the application of targeted exposomic investigations. Such context holds promise for biomarker identification for asthma diagnosis, severity prediction, as well as clarification of pathophysiological processes. We propose an exposome as an integrated investigative approach in which comprehensive environmental media sampling, metabolomic profiling of biological samples, and second-stage investigation of biomarker relevance are considered together in an iterative process.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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